

Characterization of Repetitive Seizures Using Electronic Diary Data

OVERVIEW (FROM MANUSCRIPT)

Significance: Little is known about patterns of seizures that occur multiple times a day, (e.g. clusters or serial seizures). We provide the first analysis of population-based data characterizing seizure clusters.

Methods: Data from the on-line diary, My Epilepsy Diary, were used to define a population of 5,098 community outpatients, including 1,177 who specified time of multiple seizures in a 24-hour period.

Results: One-fourth of days with any seizures included clusters for these patients. Most days with clusters included 2 seizures, with >5 events occurring in only 10% of days. One-third of seizures occurred within 3 hours of the initial event and two-thirds within 6 hours. When more than 2 seizures occurred, the time to the next seizure decreased from an average of over 2 hours (to the 3rd event) to a quarter hour (4th to 5th event).

Conclusion: Electronic diary data have provided the first overview of cluster seizures in a large community-based population. Although limited by the self-reported and observational nature of the diary data, some general patterns emerge and can help to focus questions for future studies.

OBJECTIVE

- To describe the characteristics of seizure clusters using data from an electronic diary.

METHODS

- My Epilepsy Diary (electronic diary) Figure 1 is an anonymized web and mobile-based service available at no cost to individuals with epilepsy. The diary is available in four languages and is used in USA, Australia, Canada, Italy, France and Spain. All information is entered by the patient or family.

Definitions

- There is no standard definition of seizure clusters, although “acute repetitive seizures (ARS)” was defined for trials of rectal diazepam in the 1990s as multiple seizures during a 24-hour period in adults or a 12-hour period in children. A study of intranasal midazolam (USL261) uses a definition of no further seizures from 10 minutes to 6 hours after drug administration.

- We used a broad definition for clusters as two or more events occurring within a midnight to midnight calendar day. Another definition allowed for events during any 24 hour period.

- Events designated by the user as clusters without specific times were used to calculate prevalence of clusters, but not inter-seizure time intervals.

- Descriptive statistics (mean, SD, median) were calculated. Additional analyses were performed with t-tests using a two-tailed distribution, with the assumption of independent samples of equal variance. Outcomes included cluster prevalence and frequency, and distribution of inter-seizure time intervals.

Patients

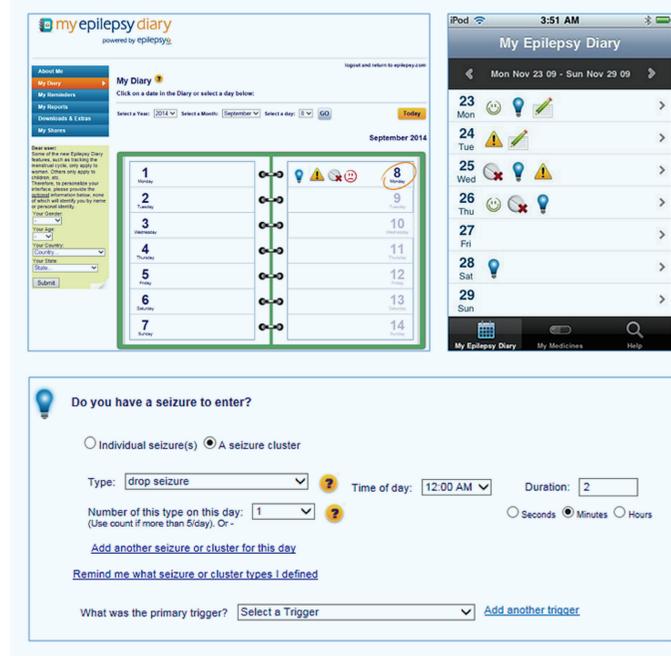
- Anonymous diary data from 28,697 patients was recorded during 2009-2014, generating 1,438,367 records. This included 546,768 patient-days (mean 70; median 19 diary days per patient).

- Full data for age and gender were not available in this de-identified data set.

- There were 5,018 patients (17.5% of all unique users) reporting 29,341 seizures occurring as clusters within 24-hour period (mean 40.6, median 7 per person).

- From this cohort, we identified 1,177 patients who recorded >2 seizures in a 24-hour period.

Figure 1. My Epilepsy Diary



RESULTS

Diary Participants

- The most common number of events on cluster days was 2 seizures per 24 hours, with declining prevalence for 3, 4, 5, 6, 7 and 8 seizures per 24 hours. Approximately 90% of days with clusters contained 5 or fewer seizures (Table 1).
- Over the course of their diary use: 1978 had only 1 cluster, 741 had 2 clusters, 437 had 3 clusters, 291 had 4 clusters and 1570 had 5 or more clusters. Outliers included 159 users reporting more than 50 seizure clusters.

Table 1. Number of Seizures Occurring a Specified Number of Times per Day

Number of Seizures in 24 hours	Number of Seizures Meeting the Criteria
2	5701
3	2226
4	1014
5	892
6	291
7	199
8	174
9	244
10	234

Seizure Frequency

- Patients with clusters had a higher daily seizure frequency (n=1,023; mean 0.14 ± 0.22) than did those who never reported >1 seizure during a 24-hour calendar day (n=2,621; mean 0.01 ± 0.20; p < 0.005).

Time Intervals Between Seizures

- The mean elapsed time from the first to the second seizure was 131 ± 149 minutes (n=6,797), 46 ± 59 minutes between the second and third events (n=2,233), 21 ± 29 minutes between the third and fourth events (n=942), and 12 ± 14 minutes between the fourth and fifth event (n=438). Among days with at least 2 seizures, one-third of the seizures occurred within 3 hours and two-thirds within 6 hours of each other. Distribution of inter-seizure intervals is shown in Table 2 and Figure 2.

Figure 2. Serial Seizure Interval. The number of Clusters Occurring Within a Specified Time Interval.

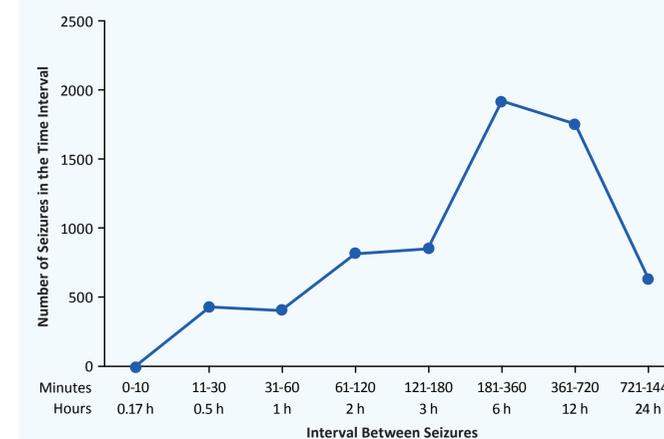
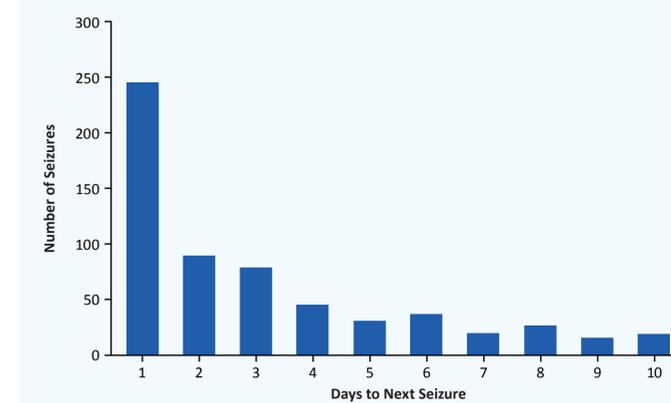


Table 2. Numbers of Sequential Seizure-Pairs Categorized by Time Interval Between Seizures

Minutes	Number of Seizures (for Days with ≥2 Seizures)	Cumulative % Less Than the Maximum Time in the Interval
<10	5	0.07%
11 - 30	438	6.4%
31 - 60	409	12.5%
61 - 120	818	24.4%
121 - 180	852	36.9%
181 - 360	1929	65.0%
361 - 720	1762	90.8%
721 - 1440	631	100%
Total Seizures	6844	100%

Figure 3. Days to Next Seizure After a Cluster



- Most sequential events occurred within 3 hr (55.6%) on 72.1% of days. After the initial event, 25.5% of sequential seizures occurred within 3 hr on 29.5% of days. Most seizure clusters are followed by a day with a single seizure (Figure 3).

- The mean time to subsequent seizures in clusters decreases with more events per episode (Table 3).

Table 3. Time to 2nd, 3rd, 4th Seizure in Cluster

Time to Next Seizure (mean minutes)	Count
1 to 2nd	131 min N = 6797
2 to 3rd	46 min N = 2233
3 to 4th	21 min N = 942
4 to 5th	12 min N = 438

- The preponderance of diary days show only one seizure, with few days documenting 5 seizures (Table 4).

Table 4. Days with 1-5 Seizures

1	28762
2	6140
3	1660
4	640
5	680
Total	37882

Modeling Alternative Definitions

- Table 5 lists a variety of definitions that could be used to define seizure clusters.

- Each change in the number of events per 24 hours or per interval results in a different prevalence.

- This model demonstrates the need for a uniformly accepted definition for seizure clusters.

Table 5. Modeling Alternative Definitions for Serial Seizures

Definition	Prevalence of Patients*	Prevalence of Patient Days
Seizures/24 h	% of Patients Having >2 Seizures in 24 Hours	% of Days on Which Seizures Occurred >2 Times
2 in 24 hours	36.5 (N = 1,865)	52.5 (N = 5,121)
3 in 24 hours	19.1 (N = 976)	19.6 (N = 1,907)
4 in 24 hours	8.4 (N = 430)	8.8 (N = 856)
5 in 24 hours	8.1 (N = 413)	7.7 (N = 750)
>6 in 24 hours	27.8 (N = 1,421)	11.4 (N = 1,112)
Total/24h	100*	100*
Seizures/h **	% of Patients Having >2 Seizures Within Interval	% of Days on Which Seizures Occurred Within Interval
>2 in 1 hour	6.8 (N = 299)	7.0 (N = 647)
>2 in 2 hours	9.7 (N = 424)	11.8 (N = 1,090)
>2 in 3 hours	9.0 (N = 395)	10.7 (N = 988)
>2 in 4 hours	8.2 (N = 357)	9.6 (N = 884)
>2 in 5 hours	7.9 (N = 344)	8.4 (N = 771)
>2 in 6-11 hours	36.9 (N = 1,614)	35.8 (N = 3,307)
>2 in >12 hours	21.6 (N = 945)	16.7 (N = 1,546)

*Patients can be counted more than once.

**Includes only seizures listed with a specific time of day in the diary.

SUMMARY

- Diary data from >28,000 patients have provided the first overview of cluster seizures in a large community-based population.

- These data reveal that 17.5% of patients using the diary experienced clusters, occurring on 13% of days when any seizure was reported.

- Days with clusters of >five events occurred in only 10% of days. One-third of seizures occurred within three hours of the initial event.

- When >2 seizures occurred, the time to the next seizure decreased from >2 hours (1st to 2nd event) to <0.25 hours (4th to 5th event).

- Further research will require a uniform definition of clusters, as shown in modeling of various definitions.

CONCLUSIONS

- Recognition of a cluster pattern may help patients prevent or protect against the next seizure. This information also helps clinicians decide whether to prescribe a rapid-acting medication as a ‘rescue treatment’.

REFERENCES

- Fisher RS, Bartfeld E, Cramer JA. Use of an online epilepsy diary to characterize repetitive seizure. *Epilepsy & Behavior* 47 (2015) 66–71.